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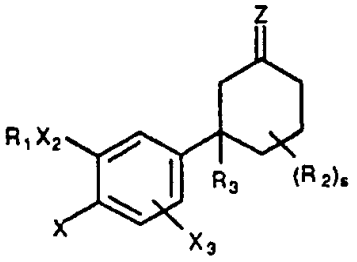
(57) Abstract

Novel cyclohexanes of Formula (I) are described herein. They inhibit the production of Tumor Necrosis Factor and are useful in the treatment of disease states mediated or exacerbated by TNF production; these compounds are also useful in the mediation or inhibition of enzymatic or catalytic activity of phosphodiesterase IV.



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COMPOUNDS, COMPOSITIONS AND TREATMENT OF ALLERGIES AND INFLAMMATION

The present invention relates to novel compounds, pharmaceutical compositions containing these compounds, and their use in treating allergic and inflammatory diseases and for inhibiting the production of Tumor Necrosis Factor (TNF).

Background of the Invention

Bronchial asthma is a complex, multifactorial disease characterized by reversible narrowing of the airway and hyperreactivity of the respiratory tract to external stimuli.

Identification of novel therapeutic agents for asthma is made difficult by the fact that multiple mediators are responsible for the development of the disease. Thus, it seems unlikely that eliminating the effects of a single mediator will have a substantial effect on all three components of chronic asthma. An alternative to the "mediator approach" is to regulate the activity of the cells responsible for the pathophysiology of the disease.

One such way is by elevating levels of cAMP (adenosine cyclic 3',5'-monophosphate). Cyclic AMP has been shown to be a second messenger mediating the biologic responses to a wide range of hormones, neurotransmitters and drugs; [Krebs Endocrinology Proceedings of the 4th International Congress Excerpta Medica, 17-29, 1973]. When the appropriate agonist binds to specific cell surface receptors, adenylate cyclase is activated, which converts Mg^{+2}-ATP to cAMP at an accelerated rate.

Cyclic AMP modulates the activity of most, if not all, of the cells that contribute to the pathophysiology of extrinsic (allergic) asthma. As such, an elevation of cAMP would produce beneficial effects including: 1) airway smooth muscle relaxation, 2) inhibition of mast cell mediator release, 3) suppression of neutrophil degranulation, 4) inhibition of basophil degranulation, and 5) inhibition of monocyte and macrophage activation. Hence, compounds that activate adenylate cyclase or inhibit phosphodiesterase should be effective in suppressing the inappropriate activation of airway smooth muscle and a wide variety of inflammatory cells. The principal cellular mechanism for the inactivation of cAMP is hydrolysis of the 3'-phosphodiester bond by one or more of a family of isozymes referred to as cyclic nucleotide phosphodiesterases (PDEs).

It has now been shown that a distinct cyclic nucleotide phosphodiesterase (PDE) isozyme, PDE IV, is responsible for cAMP breakdown in airway smooth muscle and inflammatory cells. [Torphy, "Phosphodiesterase Isozymes: Potential Targets for Novel Anti-asthmatic Agents" in New Drugs for Asthma, Barnes, ed. IBC Technical Services Ltd., 1989]. Research indicates that inhibition of this enzyme not only produces airway smooth muscle relaxation, but also suppresses degranulation of mast cells, basophils and neutrophils along with inhibiting the activation of monocytes and neutrophils. Moreover, the beneficial effects of PDE IV inhibitors are markedly potentiated when adenylate

cyclase activity of target cells is elevated by appropriate hormones or autocoids, as would be the case *in vivo*. Thus PDE IV inhibitors would be effective in the asthmatic lung, where levels of prostaglandin E_2 and prostacyclin (activators of adenylate cyclase) are elevated. Such compounds would offer a unique approach toward the pharmacotherapy of bronchial asthma and possess significant therapeutic advantages over agents currently on the market.

The compounds of this invention also inhibit the production of Tumor Necrosis Factor (TNF), a serum glycoprotein. Excessive or unregulated TNF production has been implicated in mediating or exacerbating a number of diseases including rheumatoid arthritis, rheumatoid spondylitis, osteoarthritis, gouty arthritis and other arthritic conditions; sepsis, septic shock, endotoxic shock, gram negative sepsis, toxic shock syndrome, adult respiratory distress syndrome, cerebral malaria, chronic pulmonary inflammatory disease, silicosis, pulmonary sarcoidosis, bone resorption diseases, reperfusion injury, graft vs. host reaction, allograft rejections, fever and myalgias due to infection, such as influenza, cachexia secondary to infection or malignancy, cachexia secondary to human acquired immune deficiency syndrome (AIDS), AIDS, ARC (AIDS related complex), keloid formation, scar tissue formation, Crohn's disease, ulcerative colitis, or pyresis, in addition to a number of autoimmune diseases, such as multiple sclerosis, autoimmune diabetes and systemic lupus erythematosis.

AIDS results from the infection of T lymphocytes with Human Immunodeficiency Virus (HIV). At least three types or strains of HIV have been identified, i.e., HIV-1, HIV-2 and HIV-3. As a consequence of HIV infection, T-cell-mediated immunity is impaired and infected individuals manifest severe opportunistic infections and/or unusual neoplasms. HIV entry into the T lymphocyte requires T lymphocyte activation. Viruses such as HIV-1 or HIV-2 infect T lymphocytes after T cell activation and such virus protein expression and/or replication is mediated or maintained by such T cell activation. Once an activated T lymphocyte is infected with HIV, the T lymphocyte must continue to be maintained in an activated state to permit HIV gene expression and/or HIV replication.

Cytokines, specifically TNF, are implicated in activated T-cell-mediated HIV protein expression and/or virus replication by playing a role in maintaining T lymphocyte activation. Therefore, interference with cytokine activity such as by inhibition of cytokine production, notably TNF, in an HIV-infected individual aids in limiting the maintenance of T cell activation, thereby reducing the progression of HIV infectivity to previously uninfected cells which results in a slowing or elimination of the progression of immune dysfunction caused by HIV infection. Monocytes, macrophages, and related cells, such as kupffer and glial cells, have also been implicated in maintenance of the HIV infection. These cells, like T cells, are targets for viral replication and the level of viral replication is dependent upon the activation state of the cells. [See Rosenberg *et al.*, The Immunopathogenesis of HIV Infection, Advances in Immunology, Vol. 57, 1989].

Monokines, such as TNF, have been shown to activate HIV replication in monocytes and/or macrophages [See Poli *et al.*, Proc. Natl. Acad. Sci., 87:782-784, 1990], therefore, inhibition of monokine production or activity aids in limiting HIV progression as stated above for T cells.

TNF has also been implicated in various roles with other viral infections, such as the cytomegalovirus (CMV), influenza virus, adenovirus, and the herpes virus for similar reasons as those noted.

TNF is also associated with yeast and fungal infections. Specifically *Candida albicans* has been shown to induce TNF production *in vitro* in human monocytes and natural killer cells. [See Riipi *et al.*, Infection and Immunity, 58(9):2750-54, 1990; and Jafari *et al.*, Journal of Infectious Diseases, 164:389-95, 1991. See also Wasan *et al.*, Antimicrobial Agents and Chemotherapy, 35,(10):2046-48, 1991; and Luke *et al.*, Journal of Infectious Diseases, 162:211-214,1990].

The ability to control the adverse effects of TNF is furthered by the use of the compounds which inhibit TNF in mammals who are in need of such use. There remains a need for compounds which are useful in treating TNF-mediated disease states which are exacerbated or caused by the excessive and/or unregulated production of TNF.

Summary of the Invention

This invention relates to the novel compounds of Formula (I) as shown below, useful in the mediation or inhibition of the enzymatic activity (or catalytic activity) of phosphodiesterase IV (PDE IV). These compounds also have Tumor Necrosis Factor (TNF) inhibitory activity.

This invention also relates to the pharmaceutical compositions comprising a compound of Formula (I) and a pharmaceutically acceptable carrier or diluent.

The invention also relates to a method of mediation or inhibition of the enzymatic activity (or catalytic activity) of PDE IV in mammals, including humans, which comprises administering to a mammal in need thereof an effective amount of a compound of Formula (I) as shown below.

The invention further provides a method for the treatment of allergic and inflammatory disease which comprises administering to a mammal, including humans, in need thereof, an effective amount of a compound of Formula (I).

The invention also provides a method for the treatment of asthma which comprises administering to a mammal, including humans, in need thereof, an effective amount of a compound of Formula (I).

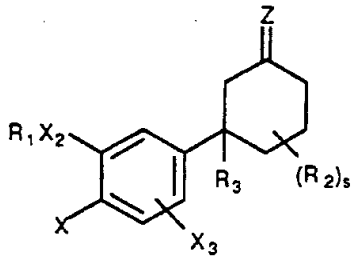
This invention also relates to a method of inhibiting TNF production in a mammal, including humans, which method comprises administering to a mammal in need of such treatment, an effective TNF inhibiting amount of a compound of Formula (I). This method may be used for the prophylactic treatment or prevention of certain TNF mediated disease states amenable thereto.

This invention also relates to a method of treating a human afflicted with a human immunodeficiency virus (HIV), which comprises administering to such human an effective TNF inhibiting amount of a compound of Formula (I).

Compounds of Formula (I) are also useful in the treatment of additional viral infections, where such viruses are sensitive to upregulation by TNF or will elicit TNF production *in vivo*.

In addition, compounds of Formula (I) are also useful in treating yeast and fungal infections, where such yeast and fungi are sensitive to upregulation by TNF or will elicit TNF production *in vivo*.

Novel compounds of this invention are represented by Formula (I):



(I)

wherein:

R_1 is $-(CR_4R_5)_nC(O)O(CR_4R_5)_mR_6$, $-(CR_4R_5)_nC(O)NR_4(CR_4R_5)_mR_6$, $-(CR_4R_5)_nO(CR_4R_5)_mR_6$, or $-(CR_4R_5)_rR_6$ wherein the alkyl moieties may be optionally substituted with one or more halogens;

m is 0 to 2;

n is 1 to 4;

r is 0 to 6;

R_4 and R_5 are independently selected hydrogen or C_{1-2} alkyl;

R_6 is hydrogen, methyl, hydroxyl, aryl, halo substituted aryl, aryloxyC_{1-3} alkyl, halo substituted aryloxyC_{1-3} alkyl, indanyl, indenyl, C_{7-11} polycycloalkyl, tetrahydrofuranyl, furanyl, tetrahydropyranyl, pyranyl, tetrahydrothienyl, thienyl, tetrahydrothiopyranyl, thiopyranyl, C_{3-6} cycloalkyl, or a C_{4-6} cycloalkyl containing one or two unsaturated bonds, wherein the cycloalkyl and heterocyclic moieties may be optionally substituted by 1 to 3 methyl groups or one ethyl group;

provided that:

a) when R_6 is hydroxyl, then m is 2; or

b) when R_6 is hydroxyl, then r is 2 to 6; or

c) when R_6 is 2-tetrahydropyranyl, 2-tetrahydrothiopyranyl, 2-tetrahydrofuranyl, or 2-tetrahydrothienyl, then m is 1 or 2; or

d) when R_6 is 2-tetrahydropyranyl, 2-tetrahydrothiopyranyl, 2-tetrahydrofuranyl, or 2-tetrahydrothienyl, then r is 1 to 6;

e) when n is 1 and m is 0, then R_6 is other than H in $-(CR_4R_5)_nO(CR_4R_5)_mR_6$;

X is YR_2, halogen, nitro, NR_4R_5, or formyl amine;

Y is O or $S(O)_{m'}$;

m' is 0, 1, or 2;

X_2 is O or NR_8;

X_3 is hydrogen or X;

R_2 is independently selected from $-CH_3$ or $-CH_2CH_3$ optionally substituted by 1 or more halogens;

s is 0 to 4;

R_3 is C_{1-4} alkyl, fluoro-substituted C_{1-4} alkyl, $CH_2NHC(O)C(O)NH_2$, $-CH=CR_{8'}R_{8'}$, cyclopropyl optionally substituted by $R_{8'}$, CN, CH_2OR_8, $CH_2NR_8R_{10}$, $C(Z')H$, $C(O)OR_8$, $C(O)NR_8R_{10}$, or $C\equiv CR_{8'}$;

Z' is O, NR_9, NOR_8, NCN, $C(-CN)_2$, CR_8CN, CR_8NO_2, $CR_8C(O)OR_8$, $CR_8C(O)NR_8R_8$, $C(-CN)NO_2$, $C(-CN)C(O)OR_9$, or $C(-CN)C(O)NR_8R_8$;

Z is O, NR_7, $NCR_4R_5C_{2-6}$ alkenyl, NOR_{14}, NOR_{15}, $NOCR_4R_5C_{2-6}$ alkenyl, NNR_4R_{14}, NNR_4R_{15}, NCN, $NNR_8C(O)NR_8R_{14}$, $NNR_8C(S)NR_8R_{14}$, $C(-CN)_2$, $CR_{14}CN$, $CR_{14}C(O)OR_8$, $CR_{14}C(O)NR_8R_{14}$, $C(-CN)NO_2$, $C(-CN)C(O)OR_9$, $C(-CN)OC(O)R_9$, $C(-CN)OR_9$, $C(-CN)C(O)NR_8R_{14}$, or =Z is 2-(1,3-dithiane), 2-(1,3-dithiolane), dimethylthio ketal, diethylthio ketal, 2-(1,3-dioxolane), 2(1,3-dioxane), 2-(1,3-oxathiolane), dimethyl ketal or diethyl ketal;

R_7 is $-(CR_4R_5)_qR_{12}$ or C_{1-6} alkyl wherein the R_{12} or C_{1-6} alkyl group is optionally substituted one or more times by C_{1-2} alkyl optionally substituted by one to three fluorines, -F, -Br, -Cl, $-NO_2$, $-Si(R_4)_3$, $-NR_{10}R_{11}$, $-C(O)R_8$, $-CO_2R_8$, $-OR_8$, -CN, $-C(O)NR_{10}R_{11}$, $-OC(O)NR_{10}R_{11}$, $-OC(O)R_8$, $-NR_{10}C(O)NR_{10}R_{11}$, $-NR_{10}C(O)R_{11}$, $-NR_{10}C(O)OR_9$, $-NR_{10}C(O)R_{13}$, $-C(NR_{10})NR_{10}R_{11}$, $-C(NCN)NR_{10}R_{11}$, $-C(NCN)SR_9$, $-NR_{10}C(NCN)SR_9$, $-NR_{10}C(NCN)NR_{10}R_{11}$, $-NR_{10}S(O)_2R_9$, $-S(O)_{m'}R_9$, $-NR_{10}C(O)C(O)NR_{10}R_{11}$, $-NR_{10}C(O)C(O)R_{10}$, thiazolyl, imidazolyl, oxazolyl, pyrazolyl, triazolyl, or tetrazolyl;

q is 0, 1, or 2;

R_{12} is C_{3-7} cycloalkyl, (2-, 3- or 4-pyridyl), pyrimidyl, pyrazolyl, (1- or 2-imidazolyl), thiazolyl, triazolyl, pyrrolyl, piperazinyl, piperidinyl, morpholinyl, furanyl, (2- or 3-thienyl), (4- or 5-thiazolyl), quinolinyl, naphthyl, or phenyl;

R_8 is independently selected from hydrogen or R_9;

$R_{8'}$ is R_8 or fluorine;

R_9 is C_{1-4} alkyl optionally substituted by one to three fluorines;

R_{10} is OR_8 or R_{11};

R_{11} is hydrogen, or C_{1-4} alkyl optionally substituted by one to three fluorines; or when R_{10} and R_{11} are as $NR_{10}R_{11}$ they may together with the nitrogen form a 5 to 7 membered ring optionally containing at least one additional heteroatom selected from O, N, or S;

R_{13} is oxazolidinyl, oxazolyl, thiazolyl, pyrazolyl, triazolyl, tetrazolyl, imidazolyl, imidazolidinyl, thiazolidinyl, isoxazolyl, oxadiazolyl, or thiadiazolyl, and each of these heterocyclic rings is connected through a carbon atom and each may be unsubstituted or substituted by one or two C_{1-2} alkyl groups;

R_{14} is hydrogen or R7; or when R8 and R_{14} are as NR_8R_{14} they may together with the nitrogen form a 5 to 7 membered ring optionally containing one or more additional heteroatoms selected from O, N, or S;

R_{15} is $C(O)R_{14}$, $C(O)NR_4R_{14}$, $S(O)_2R_7$, or $S(O)_2NR_4R_{14}$;

provided that:

(f) when Z is O, X_2 is oxygen, X_3 is hydrogen, s is 0, and X is YR_2, then R_3 is other than hydrogen;

(g) when R_{12} is N-pyrazolyl, N-imidazolyl, N-triazolyl, N-pyrrolyl, N-piperazinyl, N-piperidinyl, or N-morpholinyl, then q is not 1; or

(h) when Z is O or =Z is 2-(1,3-dioxolane) and R_3 is CH_3, CH_2OH or CH_2OC_{1-4} alkyl, then R_1X_2 is not C_1-C_3 alkoxy and X is not halogen, methoxy, ethoxy, methylthio, or ethylthio;

or a pharmaceutically acceptable salts thereof.

Detailed Description of the Invention

This invention also relates to a method of mediating or inhibiting the enzymatic activity (or catalytic activity) of PDE IV in a mammal in need thereof and to inhibiting the production of TNF in a mammal in need thereof, which comprises administering to said mammal an effective amount of a compound of Formula (I).

Phosphodiesterase IV inhibitors are useful in the treatment of a variety of allergic and inflammatory diseases including: asthma, chronic bronchitis, atopic dermatitis, urticaria, allergic rhinitis, allergic conjunctivitis, vernal conjunctivitis, eosinophilic granuloma, psoriasis, rheumatoid arthritis, septic shock, ulcerative colitis, Crohn's disease, reperfusion injury of the myocardium and brain, chronic glomerulonephritis, endotoxic shock and adult respiratory distress syndrome. In addition, PDE IV inhibitors are useful in the treatment of diabetes insipidus and central nervous system disorders such as depression and multi-infarct dementia.

The viruses contemplated for treatment herein are those that produce TNF as a result of infection, or those which are sensitive to inhibition, such as by decreased replication, directly or indirectly, by the TNF inhibitors of Formula (I). Such viruses include, but are not limited to HIV-1, HIV-2 and HIV-3, cytomegalovirus (CMV), influenza, adenovirus and the Herpes group of viruses, such as, but not limited to, *Herpes zoster* and *Herpes simplex*.

This invention more specifically relates to a method of treating a mammal, afflicted with a human immunodeficiency virus (HIV), which comprises administering to such mammal an effective TNF inhibiting amount of a compound of Formula (I).

The compounds of this invention may also be used in association with the veterinary treatment of animals, other than in humans, in need of inhibition of TNF production. TNF mediated diseases for treatment, therapeutically or prophylactically, in animals include disease states such as those noted above, but in particular viral infections. Examples of such viruses include, but are not limited to feline immunodeficiency virus (FIV) or other retroviral infection such as equine infectious anemia virus, caprine arthritis virus, visna virus, maedi virus and other lentiviruses.

The compounds of this invention are also useful in treating yeast and fungal infections, where such yeast and fungi are sensitive to upregulation by TNF or will elicit TNF production *in vivo*. A preferred disease state for treatment is fungal meningitis. Additionally, the compounds of Formula (I) may be administered in conjunction with other drugs of choice for systemic yeast and fungal infections. Drugs of choice for fungal infections, include but are not limited to the class of compounds called the polymixins, such as Polymycin B, the class of compounds called the imidazoles, such as clotrimazole, econazole, miconazole, and ketoconazole; the class of compounds called the triazoles, such as fluconazole, and itranazole, and the class of compound called the Amphotericins, in particular Amphotericin B and liposomal Amphotericin B.

The compounds of Formula (I) may also be used for inhibiting and/or reducing the toxicity of an anti-fungal, anti-bacterial or anti-viral agent by administering an effective amount of a compound of Formula (I) to a mammal in need of such treatment. Preferably, a compound of Formula (I) is administered for inhibiting or reducing the toxicity of the Amphotericin class of compounds, in particular Amphotericin B.

Preferred compounds are as follows:

When R_1 for the compounds of Formula (I) is an alkyl substituted by 1 or more halogens, the halogens are preferably fluorine and chlorine, more preferably a C_{1-4} alkyl substituted by 1 or more fluorines. The preferred halo-substituted alkyl chain length is one or two carbons, and most preferred are the moieties $-CF_3$, $-CH_2F$, $-CHF_2$, $-CF_2CHF_2$, $-CH_2CF_3$, and $-CH_2CHF_2$. Preferred R_1 substitutents for the compounds of Formula (I) are CH_2-cyclopropyl, CH_2-C_{5-6} cycloalkyl, C_{4-6} cycloalkyl, C_{7-11} polycycloalkyl, (3- or 4-cyclopentenyl), phenyl, tetrahydrofuran-3-yl, benzyl or C_{1-2} alkyl optionally substituted by 1 or more fluorines, $-(CH_2)_{1-3}C(O)O(CH_2)_{0-2}CH_3$, $-(CH_2)_{1-3}O(CH_2)_{0-2}CH_3$, and $-(CH_2)_{2-4}OH$.

When the R_1 term is (CR_4R_5), the R_4 and R_5 terms are independently hydrogen or alkyl. This allows for branching of the individual methylene units as $(CR_4R_5)_n$ or $(CR_4R_5)_m$; each repeating methylene unit is independent of the other, e.g., $(CR_4R_5)_n$ wherein n is 2 can be $-CH_2CH(-CH_3)-$, for instance. The individual hydrogen atoms of the repeating methylene unit or the branching hydrocarbon can optionally be substituted by fluorine independent of each other to yield, for instance, the preferred R_1 substitutions, as noted above.

When R_1 is a C_{7-11} polycycloalkyl, examples are bicyclo[2.2.1]-heptyl, bicyclo[2.2.2]octyl, bicyclo[3.2.1]octyl, tricyclo[5.2.1.$0^{2,6}$]decyl, etc. additional examples of which are described in Saccamano *et al.*, WO 87/06576, published 5 November 1987, whose disclosure is incorporated herein by reference in its entirety.

Preferred Z terms are O, NCN, NR_7, NOR_{14}, NOR_{15}, NNR_4R_{14}, NNR_4R_{15},$C(CN)_2$, C(-CN)OC(O)R_9, C(-CN)OR_9, $CR_{14}C(O)OR_8$, $CR_9C(O)NR_{13}R_{14}$, 2-(1,3-dithiane), dimethylthio ketal, 2-(1,3-dioxolane), or dimethyl ketal. More preferred are O, NR_7, NOR_{14}, NOR_{15}, and 2-(1,3-dioxolane).

Preferred X groups for Formula (I) are those wherein X is YR_2 and Y is oxygen. The preferred X_2 group for Formula (I) is that wherein X_2 is oxygen. The preferred X_3 group for Formula (I) is that wherein X_3 is hydrogen. Preferred R_2 groups, where applicable, is a C_{1-2} alkyl optionally substituted by 1 or more halogens. The halogen atoms are preferably fluorine and chlorine, more preferably fluorine. More preferred R_2 groups are those wherein R_2 is methyl, or the fluoro-substituted alkyls, specifically a C_{1-2} alkyl, such as a $-CF_3$, $-CHF_2$, or $-CH_2CHF_2$ moiety. Most preferred are the $-CHF_2$ and $-CH_3$ moieties.

Preferred R_3 moieties are $C(O)NH_2$, $C{\equiv}CR_8$, CN, C(Z')H, CH_2OH, CH_2F, CF_2H, and CF_3. More preferred are C≡CH and CN. Z' is preferably O or NOR_8.

Preferred R_7 moieties include optionally substituted $-(CH_2)_{1-2}$(cyclopropyl), $-(CH_2)_{0-2}$(cyclobutyl), $-(CH_2)_{0-2}$(cyclopentyl), $-(CH_2)_{0-2}$(cyclohexyl), $-(CH_2)_{0-2}$(2-, 3- or 4-pyridyl), $(CH_2)_{1-2}$(2-imidazolyl), $(CH_2)_2$(4-morpholinyl), $(CH_2)_2$(4-piperazinyl), $(CH_2)_{1-2}$(2-thienyl), $(CH_2)_{1-2}$(4-thiazolyl), and $(CH_2)_{0-2}$phenyl;

Preferred rings when R_{10} and R_{11} in the moiety $-NR_{10}R_{11}$ together with the nitrogen to which they are attached form a 5 to 7 membered ring optionally containing at least one additional heteroatom selected from O, N, or S include, but are not limited to 1-imidazolyl, 2-(R_8)-1-imidazolyl, 1-pyrazolyl, 3-(R_8)-1-pyrazolyl, 1-triazolyl, 2-triazolyl, 5-(R_8)-1-triazolyl, 5-(R_8)-2-triazolyl, 5-(R_8)-1-tetrazolyl, 5-(R_8)-2-tetrazolyl, 1-tetrazolyl, 2-tetrazloyl, morpholinyl, piperazinyl, 4-(R_8)-1-piperazinyl, or pyrrolyl ring.

Preferred rings when R_8 and R_{14} in the moiety $-NR_8R_{14}$ together with the nitrogen to which they are attached may form a 5 to 7 membered ring optionally containing at least one additional heteroatom selected from O, N, or S include, but are not limited to 1-imidazolyl, 1-pyrazolyl, 1-triazolyl, 2-triazolyl, 1-tetrazolyl, 2-tetrazolyl, morpholinyl, piperazinyl, and pyrrolyl. The respective rings may be additionally substituted, where applicable, on an available nitrogen or carbon by the moiety R_7 as described herein for Formula (I). Illustrations of such carbon substitutions includes, but is not limited to, 2-(R_7)-1-imidazolyl, 4-(R_7)-1-imidazolyl, 5-(R_7)-1-imidazolyl, 3-(R_7)-1-pyrazolyl, 4-(R_7)-1-pyrazolyl, 5-(R_7)-1-pyrazolyl, 4-(R_7)-2-triazolyl, 5-(R_7)-2-triazolyl, 4-(R_7)-1-triazolyl, 5-(R_7)-1-triazolyl, 5-(R_7)-1-tetrazolyl, and 5-(R_7)-2-tetrazolyl. Applicable nitrogen substitution by R_7 includes, but is not limited to,

1-(R7)-2-tetrazolyl, 2-(R7)-1-tetrazolyl, 4-(R7)-1-piperazinyl. Where applicable, the ring may be substituted one or more times by R7.

Preferred groups for NR_8R_{14} which contain a heterocyclic ring are 5-(R_{14})-1-tetrazolyl, 2-(R_{14})-1-imidazolyl, 5-(R_{14})-2-tetrazolyl, 4-(R_{14})-1-piperazinyl, or 4-(R_{15})-1-piperazinyl.

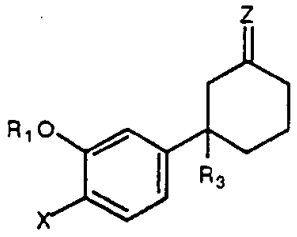
Preferred rings for R_{13} include (2-, 4- or 5-imidazolyl), (3-, 4- or 5-pyrazolyl), (4- or 5-triazolyl[1,2,3]), (3- or 5-triazolyl[1,2,4]), (5-tetrazolyl), (2-, 4- or 5-oxazolyl), (3-, 4- or 5-isoxazolyl), (3- or 5-oxadiazolyl[1,2,4]), (2-oxadiazolyl[1,3,4]), (2-thiadiazolyl[1,3,4]), (2-, 4-, or 5-thiazolyl), (2-, 4-, or 5-oxazolidinyl), (2-, 4-, or 5-thiazolidinyl), or (2-, 4-, or 5-imidazolidinyl).

When the R7 group is optionally substituted by a heterocyclic ring such as imidazolyl, pyrazolyl, triazolyl, tetrazolyl, or thiazolyl, the heterocyclic ring itself may be optionally substituted by R8 either on an available nitrogen or carbon atom, such as 1-(R8)-2-imidazolyl, 1-(R8)-4-imidazolyl, 1-(R8)-5-imidazolyl, 1-(R8)-3-pyrazolyl, 1-(R8)-4-pyrazolyl, 1-(R8)-5-pyrazolyl, 1-(R8)-4-triazolyl, or 1-(R8)-5-triazolyl. Where applicable, the ring may be substituted one or more times by R8.

Preferred are those compounds of Formula (I) wherein R_1 is -CH_2-cyclopropyl, -CH_2-C_{5-6} cycloalkyl, -C_{4-6} cycloalkyl, tetrahydrofuran-3-yl, (3- or 4-cyclopentenyl), benzyl or -C_{1-2} alkyl optionally substituted by 1 or more fluorines, and -$(CH_2)_{2-4}$ OH; R_2 is methyl or fluoro-substituted alkyl, R_3 is CN or C≡CR_8, and X is YR_2.

Most preferred are those compounds wherein R_1 is -CH_2-cyclopropyl, cyclopentyl, methyl or CF_2H; R_3 is CN or C≡CH; X is YR_2; Y is oxygen; X_2 is oxygen; X_3 is hydrogen; and R_2 is CF_2H or methyl.

A preferred subgenus of Formula (I) are the compounds of Formula (Ia)



(Ia)

wherein:

R_1 is CH_2-cyclopropyl, CH_2-C_{5-6} cycloalkyl, C_{4-6} cycloalkyl, C_{7-11} polycycloalkyl, (3- or 4-cyclopentenyl), phenyl, tetrahydrofuran-3-yl, benzyl or C_{1-2} alkyl optionally substituted by 1 or more fluorines, -$(CH_2)_{1-3}C(O)O(CH_2)_{0-2}CH_3$, -$(CH_2)_{1-3}O(CH_2)_{0-2}CH_3$, and -$(CH_2)_{2-4}$OH;

X is YR_2, halogen, nitro, NR_4R_5, or formyl amine;

Y is O or $S(O)_{m'}$;

m' is 0, 1, or 2;

R_2 is -CH_3 or -CH_2CH_3 optionally substituted by 1 or more halogens;

R_3 is C_{1-4} alkyl, halo-substituted C_{1-4} alkyl, $CH_2NHC(O)C(O)NH_2$, CN, CH_2OR_8, C(Z')H, $C(O)OR_8$, $C(O)NR_8R_{10}$, or $C{\equiv}CR_8$;

Z' is O or NOR_8;

Z is O, NR_7, NOR_{14}, NOR_{15}, NNR_4R_{14}, NNR_4R_{15}, NCN, $C(CN)_2$, C(-CN)OC(O)R_9, C(-CN)OR_9, $CR_{14}C(O)OR_8$, or =Z is 2-(1,3-dithiane), dimethylthio ketal, 2-(1,3-dioxolane), or dimethyl ketal;

R_7 is $-(CR_4R_5)_qR_{12}$ or C_{1-6} alkyl wherein the R_{12} or C_{1-6} alkyl group is optionally substituted one or more times by C_{1-2} alkyl optionally substituted by one to three fluorines, -F, -Br, -Cl, $-NO_2$, $-Si(R_4)_3$, $-NR_{10}R_{11}$, $-C(O)R_8$, $-CO_2R_8$, $-OR_8$, -CN, $-C(O)NR_{10}R_{11}$, $-OC(O)NR_{10}R_{11}$, $-OC(O)R_8$, $-NR_{10}C(O)NR_{10}R_{11}$, $-NR_{10}C(O)R_{11}$, $-NR_{10}C(O)OR_9$, $-NR_{10}C(O)R_{13}$, $-C(NR_{10})NR_{10}R_{11}$, $-C(NCN)NR_{10}R_{11}$, $-C(NCN)SR_9$, $-NR_{10}C(NCN)SR_9$, $-NR_{10}C(NCN)NR_{10}R_{11}$, $-NR_{10}S(O)_2R_9$, $-S(O)_{m'}R_9$, $-NR_{10}C(O)C(O)NR_{10}R_{11}$, $-NR_{10}C(O)C(O)R_{10}$, thiazolyl, imidazolyl, oxazolyl, pyrazolyl, triazolyl, or tetrazolyl;

q is 0, 1, or 2;

R_{12} is C_{3-7} cycloalkyl, (2-, 3- or 4-pyridyl), (1- or 2-imidazolyl), piperazinyl, morpholinyl, (2- or 3-thienyl), (4- or 5-thiazolyl), or phenyl;

R_8 is independently selected from hydrogen or R_9;

R_9 is C_{1-4} alkyl optionally substituted by one to three fluorines;

R_{10} is OR_8 or R_{11};

R_{11} is hydrogen or C_{1-4} alkyl optionally substituted by one to three fluorines; or when R_{10} and R_{11} are as $NR_{10}R_{11}$ they may together with the nitrogen form a 5 to 7 membered ring optionally containing at least one additional heteroatom selected from O, N, or S;

R_{13} is oxazolidinyl, oxazolyl, thiazolyl, pyrazolyl, triazolyl, tetrazolyl, imidazolyl, imidazolidinyl, thiazolidinyl, isoxazolyl, oxadiazolyl, or thiadiazolyl, and each of these heterocyclic rings is connected through a carbon atom and each may be unsubstituted or substituted by one or two C_{1-2} alkyl groups;

R_{14} is hydrogen or R_7; or when R_8 and R_{14} are as NR_8R_{14} they may together with the nitrogen form a 5 to 7 membered ring optionally containing one or more additional heteroatoms selected from O, N, or S;

R_{15} is $C(O)R_{14}$, $C(O)NR_4R_{14}$, $S(O)_2R_7$, or $S(O)_2NR_4R_{14}$;

provided that when R_{12} is N-imidazolyl, N-triazolyl, N-pyrrolyl, N-piperazinyl, or N-morpholinyl, then q is not 1;

or the pharmaceutically acceptable salts thereof.

An exemplified preferred compound of Formula (I) is 3-cyano-3-(cyclopentyloxy-4-methoxyphenyl)cyclohexan-1-one.

It will be recognized that some of the compounds of Formula (I) may exist in both racemic and optically active forms; some may also exist in distinct diastereomeric forms

possessing distinct physical and biological properties. All of these compounds are considered to be within the scope of the present invention.

The term "C_{1-3} alkyl", "C_{1-4} alkyl", "C_{1-6} alkyl" or "alkyl" groups as used herein is meant to include both straight or branched chain radicals of 1 to 10, unless the chain length is limited thereto, including, but not limited to methyl, ethyl, n-propyl, isopropyl, n-butyl, sec-butyl, isobutyl, *tert*-butyl, and the like.

"Alkenyl" means both straight or branched chain radicals of 1 to 6 carbon lengths, unless the chain length is limited thereto, including but not limited to vinyl, 1-propenyl, 2-propenyl, 2-propynyl, or 3-methyl-2-propenyl.

The term "cycloalkyl" or "cycloalkyl alkyl" means groups of 3-7 carbon atoms, such as cyclopropyl, cyclopropylmethyl, cyclopentyl, or cyclohexyl.

"Aryl" or "aralkyl", unless specified otherwise, means an aromatic ring or ring system of 6-10 carbon atoms, such as phenyl, benzyl, phenethyl, or naphthyl. Preferably the aryl is monocyclic, i.e, phenyl. The alkyl chain is meant to include both straight or branched chain radicals of 1 to 4 carbon atoms.

"Heteroaryl" means an aromatic ring system containing one or more heteroatoms, such as imidazolyl, triazolyl, oxazolyl, pyridyl, pyrimidyl, pyrazolyl, pyrrolyl, furanyl, or thienyl.

"Halo" means all halogens, i.e., chloro, fluoro, bromo, or iodo.

"Inhibiting the production of IL-1" or "inhibiting the production of TNF" means:

a) a decrease of excessive *in vivo* IL-1 or TNF levels, respectively, in a human to normal levels or below normal levels by inhibition of the *in vivo* release of IL-1 by all cells, including but not limited to monocytes or macrophages;

b) a down regulation, at the translational or transcriptional level, of excessive *in vivo* IL-1 or TNF levels, respectively, in a human to normal levels or below normal levels; or

c) a down regulation, by inhibition of the direct synthesis of IL-1 or TNF levels as a postranslational event.

The phrase "TNF mediated disease or disease states" means any and all disease states in which TNF plays a role, either by production of TNF itself, or by TNF causing another cytokine to be released, such as but not limited to IL-1 or IL-6. A disease state in which IL-1, for instance is a major component, and whose production or action, is exacerbated or secreted in response to TNF, would therefore be considered a disease state mediated by TNF. As TNF-ß (also known as lymphotoxin) has close structural homology with TNF-α (also known as cachectin), and since each induces similar biologic responses and binds to the same cellular receptor, both TNF-α and TNF-ß are inhibited by the compounds of the present invention and thus are herein referred to collectively as "TNF" unless specifically delineated otherwise. Preferably TNF-α is inhibited.

"Cytokine" means any secreted polypeptide that affects the functions of cells, and

is a molecule which modulates interactions between cells in immune, inflammatory, or hematopoietic responses. A cytokine includes, but is not limited to, monokines and lymphokines regardless of which cells produce them.

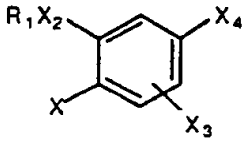
The cytokine inhibited by the present invention for use in the treatment of a HIV-infected human must be a cytokine which is implicated in (a) the initiation and/or maintenance of T cell activation and/or activated T cell-mediated HIV gene expression and/or replication, and/or (b) any cytokine-mediated disease associated problem such as cachexia or muscle degeneration. Preferrably, his cytokine is TNF-α.

All of the compounds of Formula (I) are useful in the method of inhibiting the production of TNF, preferably by macrophages, monocytes or macrophages and monocytes, in a mammal, including humans, in need thereof. All of the compounds of Formula (I) are useful in the method of inhibiting or mediating the enzymatic or catalytic activity of PDE IV and in treatment of disease states mediated thereby.

METHODS OF PREPARATION

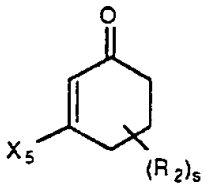
Preparing compounds of Formula (I) can be carried out by one of skill in the art according to the procedures outlined in the Examples, *infra*. The preparation of any remaining compounds of Formula (I) not described therein may be prepared by the analogous processes disclosed herein which comprise:

a) for compounds wherein X and X_3 are other than Br, I, NO_2, amine, formyl amine, or S(O)m' when m' is 1 or 2, reacting a compound of Formula (2)



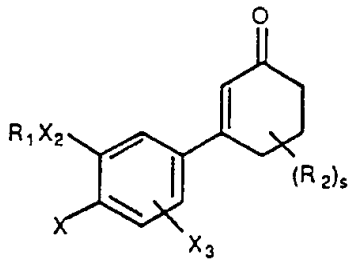
(2)

wherein R_1 represents R_1 as defined in relation to Formula (I) or a group convertable to R_1 and X represents X as defined in relation to Formula (I) or a group convertable to X and X_3 represents X_3 as defined in relation to Formula (I) or a group convertable to X_3 and X_4 is a counter ion (e.g., lithium, magnesium, etc.) with a compound of the Formula (3)



(3)

wherein X_5 is, e.g., OCH_3, OC_2H_5, $OCH(CH_3)_2$, etc., followed by appropriate workup to provide a compound of the Formula (4)



(4)

wherein R_1 represents R_1 as defined in relation to Formula (I) or a group convertable to R_1 and X represents X as defined in relation to Formula (I) or a group convertable to X and X_3 represents X_3 as defined in relation to Formula (I) or a group convertable to X_3 (see the patent application WO 9115-451-A published by WIPO). Michael-type reaction of such a compound of the Formula (4) with the appropriate precursor of R_3 then provides a compound of the Formula (1); for example, use of diethylaluminum cyanide provides a compound of the Formula (1) wherein R_1 represents R_1 as defined in relation to Formula (I) or a group convertable to R_1 and X represents X as defined in relation to Formula (I) or a group convertable to X and X_3 represents X_3 as defined in relation to Formula (I) or a group convertable to X_3 and R_3 is CN.

Compounds of Formula (I) wherein R_3 is CHO and Z is O may be prepared from the compound of Formula (I) in which R_3 is CN and Z is O after appropriate protection of the ketone as, e.g., a ketal, followed by reduction of the CN moiety with, e.g., di-isobutylaluminum hydride, followed by appropriate workup and kedif Formula (I) wherein R_3 is CH_2OH and Z is O may be prepared by reduction of the compound of Formula (I) in which R_3 is CHO and =Z is a ketal protecting group with, e.g., sodium borohydride, followed by appropriate workup and ketone deprotection.

Compounds of Formula (I) wherein R_3 is $CH_2NR_8R_8$ and Z is O may be prepared by reduction of the compound of Formula (I) in which R_3 is CN and =Z is a ketal protecting group with, e.g., lithium aluminum hydride or hydrogen in the presence of a catalyst, followed by appropriate workup, standard alkylation by R_8 and then ketone deprotection.

Compounds of Formula (I) wherein R_3 is $C{\equiv}CR_{8'}$ and Z is O may be prepared from the compound of Formula (I) in which R_3 is CHO and =Z is a ketal protecting group by reaction with a mixture of dimethyl (diazomethyl)phosphonate and potassium *t*-butoxide or other suitable base, in an inert solvent, such as tetrahydrofuran, at reduced temperature, followed by appropriate workup and ketone deprotection to provide the compounds of Formula (I) wherein R_3 is C≡CH; alternatively, prior to ketone deprotection, alkylation of the acetylene under the appropriate conditions with a strong base followed by an alkylating agent, R_8L, wherein L is a leaving group and $R_{8'}$ is not H,

followed by ketone deprotection, provides compounds of Formula (I) wherein R3 is C≡CR8'.

Compounds of Formula (I) wherein R3 is CH_2F and Z is O may be prepared from the compound of Formula (I) wherein R3 is CH_2OH and =Z is a ketal protecting group by treatment with diethyl-aminosulfur trifluoride (DAST) followed by ketone deprotection.

Compounds of Formula (I) wherein R3 is CHF_2 and Z is O may be prepared from the compound of Formula (I) wherein R3 is CHO and =Z is a ketal protecting group by treatment with diethylaminosulfur trifluoride (DAST) followed by ketone deprotection.

The compounds of Formula (I) where R3 is C_1 alkyl and Z is O may be prepared from the compound of Formula (I) wherein R3 is CH_2OH and =Z is a protected ketone by reductive removal of the alcohol with lithium in ammonia, with aluminum hydride, or by conversion of the alcohol to the corresponding thiocarbamate followed by reduction with, e.g., tributyltin hydride or trialkylsilyl hydride, and ketone deprotection; alternatively, the compounds of Formula (I) wherein R3 is C_1 alkyl and Z is O may be prepared from the compound of Formula (I) wherein R3 is CHO and =Z is a protected ketone by thioketal formation, desulfurization and ketal deprotection.

Compounds of Formula (I) where R3 is C_{2-4} alkyl or halogen substituted C_{2-4} alkyl and Z is O may be prepared by analogous deoxygenation procedures from the corresponding alcohol derived from reaction of the compound of Formula (I) wherein R3 is CHO and =Z is a protected ketone with a metal alkyl or a halogen substituted C_{2-4} metal alkyl reagent and subsequent deprotection to liberate the =Z ketone.

Compounds of Formula (I) wherein R3 is vinyl and Z is O may be prepared by, e.g., Wittig or other olefination reaction of the compound of Formula (I) wherein R3 is CHO and =Z is a protected ketone, and subsequent deprotection to liberate the =Z ketone.

Compounds of Formula (I) wherein R3 is cyclopropyl and Z is O may be prepared from the compound of Formula (I) wherein R3 is vinyl and =Z is a protected ketone by reaction with, e.g., methylene iodide and zinc-copper couple, with subsequent deprotection to liberate the =Z ketone.

Most compounds of Formula (I) wherein Z is not O are prepared from the corresponding compounds of Formula (I) wherein Z is O by reaction with the appropriate amine, alcohol, active methylene reagent, thiol, etc., in the presence of a catalyst or with removal of water, if required, as described in United States patent application 07/862,083 filed 2 April 1992 and its progeny USSN 07/968,753 filed 30 October 1992; however, when R3 is CHO, this R3 group may require protection as, e.g., a ketal, during reaction followed by deprotection.

b) Compounds of Formula (I) wherein X or X3 is formyl amine and Z is O may be prepared by formylating, at the last step, a compound wherein =Z is a protected ketone and X is NH_2, obtained by removal of a protecting group from the amine functionality; such protective groups are well known to those skilled in the art, See

Greene, T. and Wuts, P.G.M., Protecting Groups in Organic Synthesis, 2nd Ed., John Wiley and Sons, New York (1991).

c) Compounds of Formula (I) wherein X or X_3 is Br or I and Z is O may be prepared from a similarly deprotected amine by diazotization of the amine and diazonium displacement via Sandmeyer reaction.

d) Compounds of Formula (I) wherein X or X_3 is NO_2 and Z is O may be prepared from a similarly deprotected amine by oxidation of the amine to the nitro group.

e) Compounds of Formula (I) wherein Y is S(O)m' when m' is 1 or 2 and Z is O may be prepared from the compounds of Formula (I) wherein Y is S by oxidation of the SR_2 moiety under conditions well known to those skilled in the art.

The following examples are set out to illustrate how to make the compounds of this invention and methods for determining associated therapeutic activity. These examples are not intended to limit the invention in any manner, their purpose is illustrative rather than limiting.

EXAMPLE 1

Preparation of 3-cyano-3-(cyclopentyloxy-4-methoxyphenyl)cyclohexan-1-one

1a. 3-(3-cyclopentyloxy-4-methoxyphenyl)cyclohex-2-en-1-one

n-Butyllithium (2.5 M in hexanes, 15.5 mL, 38.9 mmol) was added dropwise over 30 min to a solution of 3-cyclopentyloxy-4-methoxybromobenzene (10 g, 37 mmol,) in dry tetrahydrofuran (100 mL) at -78°C under an argon atmosphere. After 1.5 h, this solution was cannulated into a solution of 3-methoxycyclohex-2-enone (4.62g, 37.4 mmol, prepared as in Pearson, A.J.; Richards, I.C.; Gardner, D.V. J. Org. Chem. 1984, 49, 3887-3891) in dry tetrahydrofuran (50 mL) at 0°C under an argon atmosphere. After 2 h at room temperature, a mixture of ether and water was added, the aqueous layer was extracted three times with ether, the combined extract was washed with water and brine, was dried (magnesium sulfate) and was evaporated. Trituration from ether/hexanes provided an off-white solid (7.33 g, 68%). Further purification of the mother liquor by flash chromatography, eluting with 1:3 ethyl acetate/hexanes, followed by trituration from ether/hexanes, provided a white solid (1.59 g, 7%). mp 89-90°C. Anal. ($C_{18}H_{22}O_3 \cdot 1/8$ H_2O) calcd: C 74.91, H 7.77; found: C 74 96, H 7.76.

1b 3-cyano-3-(cyclopentyloxy-4-methoxyphenyl)cyclohexan-1-one

To a solution of 3-(3-cyclopentyloxy-4-methoxyphenyl)cyclohex-2-en-1-one (1.46 g, 5.10 mmol) in dry toluene (45 mL) at room temperature under an argon atmosphere was added over 5 min diethylaluminumcyanide (1.0 M solution in toluene, 15.5 mL, 15.5 mmol). After 6 h, the reaction was carefully quenched with sodium hydroxide (2 N, 75 mL, 150 mmol), was extracted three times with methylene chloride, the extract was dried (magnesium sulfate) and was evaporated. Purification by flash chromatography, eluting with 1:4 ethyl acetate/hexanes, provided a pale yellow solid (1.20 g, 75%). mp 110-111°C. Anal. ($C_{19}H_{23}NO_3 \cdot 1/8$ H_2O) calcd: C 72.30, H 7.42, N 4.44; found: C 72.24, H

7.45, N 4.58.

METHODS OF TREATMENT

In order to use a compound of Formula (I) or a pharmaceutically acceptable salt thereof for the treatment of humans and other mammals, it is normally formulated in accordance with standard pharmaceutical practice as a pharmaceutical composition.

The compounds of Formula (I), or a pharmaceutically acceptable salt thereof can be used in the manufacture of a medicament for the prophylatic or therapeutic treatment of any disease state in a human or other mammal which is mediated by inhibition of PDE IV, such as but not limited to asthma, allergic, or inflammatory diseases. The compounds of Formula (I) are administered in an amount sufficient to treat such a disease in a human or other mammal.

For the purposes herein all methods of treatment and dosage regimens apply equally to both the compounds of Formula (I).

In order to use a compound of Formula (I), or a pharmaceutically acceptable salt thereof for the treatment of humans and other mammals, it is normally formulated in accordance with standard pharmaceutical practice as a pharmaceutical composition.

The amount of a compound of Formula (I) required for therapeutic effect on topical administration will, of course, vary with the compound chosen, the nature and severity of the condition and the animal undergoing treatment, and is ultimately at the discretion of the physician.

The daily dosage regimen for oral administration is suitably about .001 mg/kg to 100mg/kg, preferably 0.01 mg/Kg to 40 mg/Kg, of a compound of Formula (I) or a pharmaceutically acceptable salt thereof calculated as the free base. The active ingredient may be administered from 1 to 6 times a day, sufficient to exhibit activity.

No toxic effects are expected when these compounds are administered in accordance with the present invention.

UTILITY EXAMPLES

EXAMPLE A

Inhibitory effect of compounds of Formula (I) on *in vitro* TNF production by human monocytes

The inhibitory effect of compounds of Formula (I) on *in vitro* TNF production by human monocytes may be determined by the protocol as described in Badger *et al.*, EPO published Application 0 411 754 A2, February 6, 1991, and in Hanna, WO 90/15534, December 27, 1990.

EXAMPLE B

Two models of endotoxic shock have been utilized to determine *in vivo* TNF activity for the compounds of Formula (I). The protocol used in these models is described in Badger *et al.*, EPO published Application 0 411 754 A2, February 6, 1991, and in Hanna, WO 90/15534, December 27, 1990.

The compound of Example 1 herein demonstrated a positive *in vivo* response in reducing serum levels of TNF induced by the injection of endotoxin.

EXAMPLE C

Isolation of PDE Isozymes

The phosphodiesterase inhibitory activity and selectivity of the compounds of Formula (I) can be determined using a battery of five distinct PDE isozymes. The tissues used as sources of the different isozymes are as follows: 1) PDE Ib, porcine aorta; 2) PDE Ic, guinea-pig heart; 3) PDE III, guinea-pig heart; 4) PDE IV, human monocyte; and 5) PDE V (also called "Ia"), canine trachealis. PDEs Ia, Ib, Ic and III are partially purified using standard chromatographic techniques [Torphy and Cieslinski, Mol. Pharmacol., 37:206-214, 1990]. PDE IV is purified to kinetic homogeneity by the sequential use of anion-exchange followed by heparin-Sepharose chromatography [Torphy *et al.*, J. Biol. Chem., 267:1798-1804, 1992].

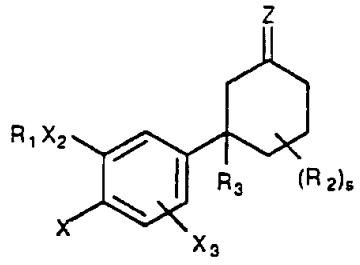
Phosphodiesterase activity is assayed as described in the protocol of Torphy and Cieslinski, Mol. Pharmacol., 37:206-214, 1990. Positive IC_{50}'s in the nanomolar to μM range for compounds of the workings examples described herein for Formula (I) have been demonstrated.

EXAMPLE D

The ability of selected PDE IV inhibitors to increase cAMP accumulation in intact tissues is assessed using U-937 cells, a human monocyte cell line that has been shown to contain a large amount of PDE IV. To assess the activity of PDE IV inhibition in intact cells, nondifferentiated U-937 cells (approximately 10^5 cells/reaction tube) were incubated with various concentrations (0.01-1000 μM) of PDE inhibitors for one minute and 1μM prostaglandin E2 for an additional four minutes. Five minutes after initiating the reaction, cells were lysed by the addition of 17.5% perchloric acid, the pH was neutralized by the addition of 1M potassium carbonate and cAMP content was assessed by RIA. A general protocol for this assay is described in Brooker *et al.*, Radioimmunassay of cyclic AMP and cyclic GMP., Adv. Cyclic Nucleotide Res., 10:1-33, 1979. The compounds of the working examples as described herein for Formula (I) have demonstrated a positive EC_{50}s in the μM range in the above assay.

What is claimed is:

1. A compound of formula (I):



(I)

wherein:

R_1 is $-(CR_4R_5)_nC(O)O(CR_4R_5)_mR_6$, $-(CR_4R_5)_nC(O)NR_4(CR_4R_5)_mR_6$, $-(CR_4R_5)_nO(CR_4R_5)_mR_6$, or $-(CR_4R_5)_rR_6$ wherein the alkyl moieties may be optionally substituted with one or more halogens;

m is 0 to 2;

n is 1 to 4;

r is 0 to 6;

R_4 and R_5 are independently selected hydrogen or C_{1-2} alkyl;

R_6 is hydrogen, methyl, hydroxyl, aryl, halo substituted aryl, aryloxyC_{1-3} alkyl, halo substituted aryloxyC_{1-3} alkyl, indanyl, indenyl, C_{7-11} polycycloalkyl, tetrahydrofuranyl, furanyl, tetrahydropyranyl, pyranyl, tetrahydrothienyl, thienyl, tetrahydrothiopyranyl, thiopyranyl, C_{3-6} cycloalkyl, or a C_{4-6} cycloalkyl containing one or two unsaturated bonds, wherein the cycloalkyl and heterocyclic moieties may be optionally substituted by 1 to 3 methyl groups or one ethyl group;

provided that:

a) when R_6 is hydroxyl, then m is 2; or

b) when R_6 is hydroxyl, then r is 2 to 6; or

c) when R_6 is 2-tetrahydropyranyl, 2-tetrahydrothiopyranyl, 2-tetrahydrofuranyl, or 2-tetrahydrothienyl, then m is 1 or 2; or

d) when R_6 is 2-tetrahydropyranyl, 2-tetrahydrothiopyranyl, 2-tetrahydrofuranyl, or 2-tetrahydrothienyl, then r is 1 to 6;

e) when n is 1 and m is 0, then R_6 is other than H in $-(CR_4R_5)_nO(CR_4R_5)_mR_6$;

X is YR_2, halogen, nitro, NR_4R_5, or formyl amine;

Y is O or $S(O)_{m'}$;

m' is 0, 1, or 2;

X_2 is O or NR_8;

X_3 is hydrogen or X;

R_2 is independently selected from $-CH_3$ or $-CH_2CH_3$ optionally substituted by 1 or more halogens;

s is 0 to 4;

R_3 is C_{1-4} alkyl, fluoro-substituted C_{1-4} alkyl, $CH_2NHC(O)C(O)NH_2$, -CH=$CR_8'R_8'$, cyclopropyl optionally substituted by R_8', CN, CH_2OR_8, $CH_2NR_8R_{10}$, C(Z')H, $C(O)OR_8$, $C(O)NR_8R_{10}$, or C≡CR_8';

Z' is O, NR_9, NOR_8, NCN, $C(\text{-CN})_2$, CR_8CN, CR_8NO_2, $CR_8C(O)OR_8$, $CR_8C(O)NR_8R_8$, $C(\text{-CN})NO_2$, $C(\text{-CN})C(O)OR_9$, or $C(\text{-CN})C(O)NR_8R_8$;

Z is O, NR_7, $NCR_4R_5C_{2-6}$ alkenyl, NOR_{14}, NOR_{15}, $NOCR_4R_5C_{2-6}$ alkenyl, NNR_4R_{14}, NNR_4R_{15}, NCN, $NNR_8C(O)NR_8R_{14}$, $NNR_8C(S)NR_8R_{14}$, $C(\text{-CN})_2$, $CR_{14}CN$, $CR_{14}C(O)OR_8$, $CR_{14}C(O)NR_8R_{14}$, $C(\text{-CN})NO_2$, $C(\text{-CN})C(O)OR_9$, $C(\text{-CN})OC(O)R_9$, $C(\text{-CN})OR_9$, $C(\text{-CN})C(O)NR_8R_{14}$, or =Z is 2-(1,3-dithiane), 2-(1,3-dithiolane), dimethylthio ketal, diethylthio ketal, 2-(1,3-dioxolane), 2(1,3-dioxane), 2-(1,3-oxathiolane), dimethyl ketal or diethyl ketal;

R_7 is $-(CR_4R_5)_qR_{12}$ or C_{1-6} alkyl wherein the R_{12} or C_{1-6} alkyl group is optionally substituted one or more times by C_{1-2} alkyl optionally substituted by one to three fluorines, -F, -Br, -Cl, $-NO_2$, $-Si(R_4)_3$, $-NR_{10}R_{11}$, $-C(O)R_8$, $-CO_2R_8$, $-OR_8$, -CN, $-C(O)NR_{10}R_{11}$, $-OC(O)NR_{10}R_{11}$, $-OC(O)R_8$, $-NR_{10}C(O)NR_{10}R_{11}$, $-NR_{10}C(O)R_{11}$, $-NR_{10}C(O)OR_9$, $-NR_{10}C(O)R_{13}$, $-C(NR_{10})NR_{10}R_{11}$, $-C(NCN)NR_{10}R_{11}$, $-C(NCN)SR_9$, $-NR_{10}C(NCN)SR_9$, $-NR_{10}C(NCN)NR_{10}R_{11}$, $-NR_{10}S(O)_2R_9$, $-S(O)_{m'}R_9$, $-NR_{10}C(O)C(O)NR_{10}R_{11}$, $-NR_{10}C(O)C(O)R_{10}$, thiazolyl, imidazolyl, oxazolyl, pyrazolyl, triazolyl, or tetrazolyl;

q is 0, 1, or 2;

R_{12} is C_{3-7} cycloalkyl, (2-, 3- or 4-pyridyl), pyrimidyl, pyrazolyl, (1- or 2-imidazolyl), thiazolyl, triazolyl, pyrrolyl, piperazinyl, piperidinyl, morpholinyl, furanyl, (2- or 3-thienyl), (4- or 5-thiazolyl), quinolinyl, naphthyl, or phenyl;

R_8 is independently selected from hydrogen or R_9;

R_8' is R_8 or fluorine;

R_9 is C_{1-4} alkyl optionally substituted by one to three fluorines;

R_{10} is OR_8 or R_{11};

R_{11} is hydrogen, or C_{1-4} alkyl optionally substituted by one to three fluorines; or when R_{10} and R_{11} are as $NR_{10}R_{11}$ they may together with the nitrogen form a 5 to 7 membered ring optionally containing at least one additional heteroatom selected from O, N, or S;

R_{13} is oxazolidinyl, oxazolyl, thiazolyl, pyrazolyl, triazolyl, tetrazolyl, imidazolyl, imidazolidinyl, thiazolidinyl, isoxazolyl, oxadiazolyl, or thiadiazolyl, and each of these heterocyclic rings is connected through a carbon atom and each may be unsubstituted or substituted by one or two C_{1-2} alkyl groups;

R_{14} is hydrogen or R_7; or when R_8 and R_{14} are as NR_8R_{14} they may together with the nitrogen form a 5 to 7 membered ring optionally containing one or more additional heteroatoms selected from O, N, or S;

R_{15} is $C(O)R_{14}$, $C(O)NR_4R_{14}$, $S(O)_2R_7$, or $S(O)_2NR_4R_{14}$;

provided that:

(f) when Z is O, X_2 is oxygen, X_3 is hydrogen, s is 0, and X is YR_2, then R_3 is other than hydrogen;

(g) when R_{12} is N-pyrazolyl, N-imidazolyl, N-triazolyl, N-pyrrolyl, N-piperazinyl, N-piperidinyl, or N-morpholinyl, then q is not 1; or

(h) when Z is O or =Z is 2-(1,3-dioxolane) and R_3 is CH_3, CH_2OH or CH_2OC_{1-4} alkyl, then R_1X_2 is not C_1-C_3 alkoxy and X is not halogen, methoxy, ethoxy, methylthio, or ethylthio;

or a pharmaceutically acceptable salts thereof.

2. A compound according to claim 1 which is 3-cyano-3-(cyclopentyloxy-4-methoxyphenyl)cyclohexan-1-one.

3. A pharmaceutical composition comprising a compound of Formula (I) according to claim 1 and a pharmaceutically acceptable excipient.

4. A method for treating an allergic or inflammatory state which method comprises administering to a subject in need thereof an effective amount of a compound of Formula (I) according to claim 1 alone or in combination with a pharmaceutically acceptable excipient.

INTERNATIONAL SEARCH REPORT

Int. ..ational application No.
PCT/US94/10815

A. CLASSIFICATION OF SUBJECT MATTER
IPC(6) :A61K 31/275; C07C 255/46
US CL :514/520; 558/426
According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 514/520; 558/426

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X --- Y	Chem. Pharm. Bull., Vol. 24(7), issued 1976, Takeda et al, "Azabicycloalkanes as analgetics. II 1)An improved synthesis of 1-phenyl-6-azabicyclo(3,2,1)-octane derivatives", pages 1514-1526, see page 1515 compound 3(h), in Chart I.	1-4 ----- 1-4

☐ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

*	Special categories of cited documents:	"T"	later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
"A"	document defining the general state of the art which is not considered to be of particular relevance	"X"	document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"E"	earlier document published on or after the international filing date	"Y"	document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"L"	document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)	"&"	document member of the same patent family
"O"	document referring to an oral disclosure, use, exhibition or other means		
"P"	document published prior to the international filing date but later than the priority date claimed		

Date of the actual completion of the international search 18 JANUARY 1995	Date of mailing of the international search report JAN 27 1995
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703) 305-3230	Authorized officer JOSEPH PAUL BRUST Telephone No. (703) 308-1235

Form PCT/ISA/210 (second sheet)(July 1992)*

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US94/10815

BOX I. OBSERVATIONS WHERE CLAIMS WERE FOUND UNSEARCHABLE

2. Where no meaningful search could be carried out, specifically:

Aside from the specific structure 3-CYANO-3-(CYCLOPENTYLOXY-4-METHOXY PHENYL CYCLOHEXAN-1-ONE (the single compound specifically described at page 15, lines 16 and in claim 2, compounds with clearly defined structures, the terms used in the unsearchable claims cannot be ascertained into meaningful enough specific compound structures such as to afford a determination of proper specific subclasses to search. Thus, the unsearchable claims will be searched only to the extent they read on searchable features (the above compounds) in the description and claims.